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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/056,343	04/07/1998	UFFE LOEVBORG	3556.224-US	5207

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EXAMINER
MOORE, WILLIAM W

ART UNIT	PAPER NUMBER
1652	30

DATE MAILED: 07/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/056,343	LOEVBORG, UFFE	
	Examiner	Art Unit	
	William W. Moore	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *77-96* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *77-96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Amendment

Applicant's Amendment G, Paper No. 28 filed May 22, 2003, has been entered, canceling claims 48-66 and amending claim 77, because the claim amendment resolves one element of an indefinite description in the claim. Claims 77-96 are now pending in the instant application, but reconsideration of the nature of the disclosure of the instant specification, by comparison with the subject matter described in the claims, necessitates the following new grounds of rejection and this communication is therefore not made final.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 77-96 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification fails to exemplify or describe the practice of the subject matters of the methods of claims 77 and 87, and the dependent claims 78-86 and 88-96 fail to improve the aberrant description provided in the independent claim 77 and 87 of the methods that the specification does exemplify and describe. The description of the methods recited by the claims is aberrant because the specification actually exemplifies and describes methods of screening, or selection, or identification, among multiple, variegated, polypeptide products – products that result from variegation at the level of an encoding DNA sequence as the first process in a disclosed method – to evaluate the immunogenicity of the variegated products wherein proposed or actual epitopes in the amino acid sequence of the reference protein are altered and an animal's immune response to the variegated polypeptides is assessed, whereby one or more variegated polypeptide products are

identified as providing reduced immunogenicity in an animal. Yet both of claims 77 and 87 contrarily describe methods "for producing a DNA molecule encoding a [less immunogenic] variant of a reference protein", methods which culminate, in clause (d) of claim 77 and in clause (c) of claim 87, in "forming a DNA molecule encoding the amino acid sequence of a selected variant". These ultimate steps follow, where the preambles of claims 77 and 87 recite the open conjunction "comprising", the initial preparation of multiple DNA molecules encoding multiple variants of a reference protein – because the specification does not disclose or suggest any other way of preparing a multitude of multiple variants – thus the final process described by the claims is, in reality, an early, if not initial, process of methods the specification actually discloses. "While one does not need to have carried out one's invention before filing a patent application, one does need to be able to describe that invention with particularity" to satisfy the description requirement of the first paragraph of 35 U.S.C. §112. *Fiers v. Revel v. Sugano*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). Where the specification furnishes no particular description of the methods that are described, in a reverse ordering of the necessary process, by claims 77-96, its treatment of the claimed subject matter entirely prospective where skilled artisans in the relevant field of immunology would have formed the DNA molecules according to the terminal clauses of claims 77 and 87 at the outset of the practice of a method disclosed by the specification.

The following is a quotation of the second paragraph of 35 U.S.C. §112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 77-96 are rejected under35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 77 and 87 are also rejected under the second paragraph of 35 U.S.C. §112 because they are indefinite in the circuitous description they provide of the recapitulation

of a process step as a terminal step in a process where the process step must have already occurred early in a method, or at the outset of a method, for achieving a certain, useful, result. Claims 78-86 and 88-96 are included in this rejection of the claims from which they depend because they fail to clarify the ambiguity of claims 77 and 87.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 77-79, 85-90, 95 and 96 are rejected, essentially for reasons of record, under 35 U.S.C. §103(a) as being unpatentable over Ladner et al., U.S. 5,223,409, of record.

Applicant's arguments filed May 22, 2003, have been fully considered with respect to the amended claim 77 and claims 78, 79, 85-89, 95 and 96 dependent thereon, but they are not persuasive. This rejection is based solely on the application of the teachings of Ladner et al. under 35 U.S.C. §103(a), thus differs from the corresponding rejection of record of claims 77-79, 85-90, 95 and 96. Applicant suggested in Paper No. 22 filed October 9, 2002, that the disclosure of Ladner et al. of modification of the amino acid sequence of a polypeptide, the medicinally active enzyme streptokinase, that is "antigenic to an undesirable extent" to produce a variant polypeptide with reduced allergenicity is deficient because Ladner et al. (1) map antigenic epitopes generally during their screening procedure, rather than specifically, *a priori*, (2) do not explicitly state that that a resulting, epitope-reduced, streptokinase be functional, and, (3) do not require that the IgE response to the altered, epitope-reduced, enzyme be reduced to render it less allergenic in animals.

In the latter arguments, Applicant had relied on limitations absent from the claims, but clause (c) of claim 77 and clause (b) of claim 87 now require that one or more epitopes be mapped by immunological "and proteochemical" techniques. Neither the preambles of

claims 77 and 87, nor the order of the processes recited in these claims, require that (an) epitope(s) of the reference protein be identified – mapped – before variants of a reference protein are produced in clause (a) of claim 77 or produced for incubation with antibodies in clauses (b)(i) and (b)(ii) of claim 87. Ladner et al. therefore remains prior art under 35 U.S.C. §103(a) where it is clear from the teachings of Ladner et al. that they were aware that antigenic epitopes were present in the structure of streptokinase and also aware that their processes, comprising preparation of DNA molecules encoding variants of the reference streptokinase polypeptide, would identify regions that contribute to antigenicity, i.e., epitopes, and reduce the antigenicity of streptokinase, thus achieving the same result indicated in the closing phrases of the final clauses of methods of claims 77 and 78.

No claimed method yet requires that a DNA molecule encode a variant that has the full, or even a partial, biological activity of the reference protein, only that the molecule encode a less antigenic variant and even if a limitation as to function were introduced in claims 48, 58, 77, and 87, Ladner et al. disclose, col. 103, lines 6-8, that "mutants are tested to verify that the [desired] properties have not been altered to an unacceptable degree by the mutations". No claimed method yet requires that a particular kind of epitope, such as an IgE epitope, be identified in reference proteins for modifications that would reduce allergenicity in a variant, only that a generic "lower immunogenic response" be invoked in animals exposed to variants. The first step of the process taught by Ladner et al. is preparation of DNA segments encoding several "Initial Potential Binding Domains" [IPBDs] that constitute consecutive, undesirably antigenic, regions of a polypeptide, thus permits reduction of an immune system response caused by any kind of epitope in persons or animals exposed to a variant relative to the response to an unaltered reference protein.

Claim 77 also differs further from the claims subject to the rejection of record based on teachings of Ladner et al. in requiring that antibodies raised to a reference protein and

at one or more variants be incubated with both the reference protein and one or more variants. The claimed process would still have been obvious over the teachings of Ladner et al. because it would have been obvious to one of ordinary skill in the art at the time the invention was made to confirm the reduced immunogenicity of at least one variant, as indicated by incubation with antibodies to the reference protein, by conducting the reference protein with antisera to the variant to establish that antigenicity of the primary epitope was reduced. This is a standard control process step.

Because the present claim recitations do not correspond to the actual disclosure of the specification, as explained at pages 2 and 3 above, no claimed method specifically excludes the piecemeal method of Ladner et al. wherein DNA segments specifying variegated epitope regions are comprised within multiple conveying DNA sequences, expression vectors, termed "Genetic Package[s]" [GP], permitting a host cell maintaining a GP to display each variegated PBD peptide on the surface of an expressed carrier molecule, a coat protein of a bacteriophage. While Ladner et al. do not use the term "epitope", the artisan reading their disclosure would recognize that the "antigenic determinants" which Ladner et al. discuss, i.e., the native IPBDs that bind most effectively in their method to a detecting antibody surface, are epitopes.

Claims 87-89, 95 and 96 are included in this rejection because, even though a process using as series of monoclonal antibodies is preferred by Ladner et al. is preferred, the disclosure of Ladner et al. of a further steps of contacting both the several native, IPBDs and their corresponding, variegated, PBDs with a surface covered with antibodies raised in a subject to the polypeptide that is undesirably antigenic may be a contacting, col. 103, lines 9-30, with polyclonal antisera in a recursive process that includes a composite assessment of the binding affinity of each of the carrier molecule-displayed IPBDs, and the binding affinities of their corresponding variegated PBDs, to determine which peptide

sequences of the variegated PBDs bind with reduced affinity to the antibody-covered surface and selection of those sequences that bind with reduced affinity as replacements for the corresponding peptide region of the undesirably antigenic polypeptide.

Ladner et al. are considered to have rendered the methods of claims 77-79, 85-89, 95 and 96, obvious to one of ordinary skill in the art at the time the invention was made because they teach each step needed to practice a method set forth in the claims in a way will provide results the claims describe even though the claims fail to describe a disclosed method, teach a medicinal polypeptide known to evoke an immunogenic response in animals that would be more efficacious were its immunogenicity lowered, thus providing motivation to do so, and also disclose many examples of practicing each step of the method taught in section "V.R." elsewhere in the patent, with other polypeptides and their encoding DNAs, thus providing a reasonable expectation of success in practicing their methods to an artisan at that time. Thus the claimed methods embrace a scope of subject matter obvious over the disclosure of Ladner et al.

Claims 80-84 and 90-94 are rejected, essentially for reasons of record, under 35 U.S.C. §103(a) as obvious over Ladner et al., U.S. 5,223,409, as applied to claims 77-79, 85-90, 95 and 96 above, in view of either Zacharaiae et al., 1981, Allergy, Vol. 36, pages 513-516, or Arlian et al., 1990, International Archives of Allergy and Applied Immunology, Vol. 91, pages 278-284, both of record.

Claims 83, 84, 93, and 94 are included in this rejection because the claim limitation "process enzyme" in claims 83 and 93 cannot be considered to distinguish a reference polypeptide subject to the corresponding rejection of record of "detergent enzyme" of claims 81 and 91 where claims 82 and 84, as well as claims 92 and 94, make it clear that the same enzyme may be both a "detergent" and a "process" enzyme. Applicant's arguments filed October 9, 2002, have again been fully considered with respect to claims 80-84 and 90-94, but they are not persuasive. Applicant had suggested in Paper No. 22 that the absence of a teaching of a specific DNA sequence in either of Zacharaiae et al. or Arian et al., renders them inapplicable as prior art, but, as noted in Paper No. 21 mailed

April 9, 2002, the claims require no particular amino acid sequence for a reference protein, do not require that a particular epitope region be altered in any reference protein, require no particular amino acid sequence modification to reduce allergenicity and amino acid sequences of the detergent proteases Alcalase® and Esperase® taught by Zacharaiae et al. to cause IgE antibody-mediated sensitization in persons, resulting in chronic, symptoms of respiratory irritation, coughing, shortness of breath, and chest tightening serine proteases and the amino acid sequences of the detergent proteases Alcalase® and Esperase® taught by Arlian et al. to cause respiratory allergy and to exhibit specific, electropositive antigens binding significant levels of human IgE antibodies as demonstrated by crossed immunoelectrophoresis, were already know in the art at the time the invention was made.

Thus one of ordinary skill in the art would have had ample motivation at the time the invention was made to design and synthetically produce generic DNA sequences encoding each protease to permit mutation and variegation of amino acid sequences of peptide regions identified as an antigenic determinants in a method of Ladner et al., and such an artisan would have had a reasonable expectation of success in preparing a variant of any or all of these enzymes that would evoke a lowered immunogenic response in a person where suitable IgE antibodies could be isolated from exposed individuals to conduct the screening steps of Ladner et al. that identify the significant antigenic determinants and permit measuring of reduced binding to antibody to identify variegated peptides that, when replacing the antigenic determinant, or epitope, in a variant subtilisin will render the variant subtilisin capable of evoking a lowered immunogenic response in a person.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 703.308.0583. The examiner can normally be reached between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at 703.308.3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703.308.4242 for regular communications and 703.308.0294 for After Final

communications. The examiner's direct fax phone number is 703.746.3169. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703.308.0196.

5 William W. Moore

William W. Moore
July 7, 2003